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(54) **Pharmaceutical composition of microparticles with controlled release and process of preparing it**

Mikrosphäre enthaltende pharmazeutische Zusammensetzung mit kontrollierter Freigabe und Verfahren zur Herstellung

Composition pharmaceutique contenant des microparticules avec libération contrôlée et son procédé de fabrication

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DescriptionTechnical field of the invention

5 The present invention relates to the preparation of novel pharmaceutical compositions in the form of particles consisting of composite materials which can be used for the controlled release of pharmacologically active substances.

Background of the invention

10 Pharmaceutical compositions in the form of particles are known, which comprise the active agent dissolved or dispersed in a polymer and which are suitable for the delayed release of some molecules of clinical interest after one single administration. Among the biodegradable polymers used for this purpose, the polylactic acid, polyglycolic acid and copolymer thereof proved to be effective in delaying the release of the drug. Also polymers of polysaccharide type have been used to modulate the release of drugs. Among those polymers xanthan, scleroglucan, taluronic acid and chitosan
 15 proved to have good technological features and practically inexistent toxicity. Moreover some of these exhibit bioadhesive properties which render them specifically suitable to prolong the retaining time of pharmaceutical formulations in the administration sites. Both group of polymers is therefore widely used in manufacturing, for instance, microparticles comprising active agents whose release is modulated by them. Said particles systems may be prepared using techniques of emulsion whereby the active agent is dissolved or dispersed in a polymer solution and the resulting solution
 20 or dispersion is subsequently emulsified in a solvent in which the polymer is insoluble. The solvents are thereafter removed by evaporation (GB-A-2 077 693), by extraction with a second solvent (US 4 818 542) or by combination of the two techniques (BE-A-890 638). Moreover techniques may be found in the literature, which have been employed to modify the permeability and/or the biodegradation of the polymers which form the particle systems in such a way to exert an influence on the kinetic of the active agent release. For example there is described in the US patent 4 479 911
 25 the addition of an alkaline agent to the continuous phase used in preparing particle systems. Said agent increases the release rate of the active agent but the concentration range in which it may be used is limited by the higher degradation rate of the polymer in presence of alkaline agents. Moreover the use of strongly alkaline agents (e.g. sodium or potassium hydroxide) limits the applicability of said technique to hydrolysis stable medicaments. In the EP-A₁-0 204 476 the coating of nuclei of active agent with a film consisting of a biodegradable polymer and an agent promoting the formation
 30 of pores (e.g. saccharose) is disclosed. In this case the release is influenced by the porosity generated within the film by the dissolution of said agent. This involves however the use of different excipients in preparing the active agent-comprising core and brings about factors which may influence, in a poorly controllable way, the preparing process, the chemical-physical stability and the release kinetic of the active agent. Moreover the coating of said nucleus adds one further technological stage to the manufacturing of the end product, which is a drawback from the view point of the production. In the EP-A₂-0 092 918 and JP 2078 629 there is described the preparation of biodegradable block-copolymers constituted by a biodegradable hydrophobic part and an amphiphilic part capable of absorbing water and/or biological fluids to form a hydrogel able to control the release of the active agent. Such a technology involves the development of a new copolymer whose chemical nature is different from the "sum" of the chemical features of the starting products. Accordingly the biocompatibility properties of the end product are modified as well; it should moreover be considered
 40 that the usage of said product depends on the compliance with the protocols for the clearance of new products. In the EP-A₂-0 052 510 and US patent 4 675 189 there is described a process for preparing particles which involves the presence of one or more agents modifying the polymer hydrolysis in order to modulate the release of the active agent. In this case too, the presence of said agents limits the possibility of application of said technique to hydrolysis stable medicaments. Finally the preparation of a polymer mixture by co-solubilizing homo- and copolymers belonging to the polyester class is disclosed in the EP-A₁- 0 281 482; such a mixture has a degradation rate higher than the single polymers. The application of said technique is however limited to the high molecular weight medicaments only, since the permeability of the polymer is not modified, thus the diffusion of low molecular weight medicaments is not modulated. Furthermore, because of the nature of the employed polymers (high molecular weight), such a technique limits itself with regard to the relative percentage of the employed polymers, consequently affecting the flexibility of the end system.
 50 The methods according to the aforementioned literature essentially try to modify the permeability or the degradation rate of the polymer in order to modulate the rate of release of the medicament. Said methods bring about different drawbacks, such as:

- addition of agents which may modify the molecular weight of the polymer, giving rise to the degradation of the same in noncontrollable way, already in the preparation phase of the microparticles;
- addition of several stages in the preparation process of the microparticles;
- synthesis of novel copolymers whose biocompatibility properties may dramatically change with respect to the starting homopolymers, since the chemical nature of the polymers is modified;

- addition of chemical agents which may affect the stability of the active agent within the microparticles or in any case which may limit the applicability of the technology.

Summary of the invention

Novel pharmaceutical compositions in the form of particles have now been found, which are able to overcome the drawbacks of the known prior art. Said pharmaceutical compositions comprise a biodegradable polymer consisting of co-poly(lactic-glycolic) acid, an amphiphilic polymer consisting of polyethylene glycol, an agent modifying the interface properties of the particles and a pharmacologically active substance. The preparation of such compositions comprises :

- the co-solubilization of the polymeric constituents with the agent modifying the interface properties in presence of solvents, if any;
- the solution or suspension of the active substance in the mixture of the polymeric compounds;
- the formation of particles consisting of the polymers, the agent modifying the interface properties and the active substance by techniques of emulsion or extrusion or spray-drying or spray-congealing. The thus obtained particles exhibit improved biocompatibility properties and allow a delayed release of the active substance.

Detailed description of the invention

The features and advantages of the pharmaceutical compositions according to the present invention and the process for preparing the same will be more clearly evidenced by the following detailed description. As the first stage in preparing one of the formulations a biodegradable polymer consisting of co-poly(lactic-glycolic) acid, an amphiphilic polymer consisting of polyethylene glycol and an agent modifying the interface properties are co-solubilized. This manufacturing method proved to be particularly useful since it avoids the environmental problems and those problems concerning the potential toxicity of the solvents. As an alternative option, the polymers and the agent modifying the interface properties may be solubilized in the minimum necessary amount of solvent or solvent mixture. A pharmacologically active substance is then dissolved or dispersed in the polymer solution and the resulting solution or dispersion is emulsified by shaking in a suitable dispersing phase comprising agents able to modify the surface properties of the particles. In order to avoid the diffusion of the amphiphilic polymeric component into the dispersing phase of the emulsion, said dispersing phase may comprise appropriate percentages of the same amphiphilic polymer. Moreover, in order to decrease the likely partition of the active substance into the dispersing phase, the pH or the ionic strength of the same phase may be modified or still mixtures of solvents may be used. The dispersing phase of the emulsion may furthermore be saturated of the active substance. The shaking necessary to emulsify is carried out for time periods and at a speed suitable to obtain a completely emulsified product. The solvent, if present at all, is removed by evaporation. The particle suspension is centrifuged and/or filtered, optionally washed and the thus obtained product is dried in vacuum, by microwaves or lyophilized. The size of the thus obtained particles is in the range 0.1-150 μm . The equipment employed for emulsifying may be an emulsifier of the type rotor-stator capable of achieving the necessary rotation speed or any other type of emulsifier able to supply to the system the necessary energy for promoting the formation of the emulsion.

Another process, which may be used to prepare the particles constituted by the compositions object of the present invention, is based on the extrusion of the mass consisting of the biodegradable polymer, the amphiphilic polymer, the agent modifying the interface properties and the active substance. The extrudible mass may be obtained by dissolving the biodegradable polymer and the agent modifying the interface properties in the amphiphilic polymer or in suitable amount of solvent. The materials may be either pre-mixed and fed into the pre-heated extruder or heated, either alone or together before the extrusion or still heated by the heat generated during the extrusion itself. The optimum of temperature changes according to the employed polymers and to the amount of solvent, if present at all. The composition is extruded and then cooled. The extruded product may be obtained in the form of particles, beads or pellets, which are then micronized to the desired size. A still further process, which may be used for preparing the compositions in the form of the particles object of the present invention involves spray-drying the mixture consisting of the polymers, the agent modifying the interface properties, the active substance and the solvent in a flow of warm air according to a classical method. As an alternative option, in the case of thermolabile active substances, the mixture may be sprayed in cold air flow (spray-congealing) to force the solvent comprised in the particles to congeal. The solvent may then be removed by lyophilisation. The particles according to the present invention may comprise a great deal of different active substances both synthetic and natural, comprising polypeptides. The following nonlimitative list shows some classes of pharmacologically active substances which may be used in the formulations of the present invention: central nervous system active medicaments, cardiovasculars, hypotensives, diuretics, antiphlogistics, analgesics, antipyretics, anti-asthma, bronchodilators, antitussives, mucolytics, antibiotics, chemotherapies, antiviruses, hormones, antineoplastics, immunosuppressors, immunostimulants, proteins, polypeptides, vaccines etc. Particularly preferred active substances are: nifedipine, diltazem, diacerein, verapamil, captopril, magesrol acetate, temazepam, nicergoline, ibuprofen, pirox-

icam, naproxen, diclofenac, broxaterol and hydrochloride thereof, salbutamol, isoproterenol, albuterol, terbutaline, theophylline, bedometasone, desamechasone. Particularly preferred active substances of polypeptide type are: vasopressin, epidermic growth factor (EGF), luliberin or luteinizing hormone-release hormone (LH-RH), LH-RH analogues, (Des-Gly, D-Trp⁶, Pro⁹-ethylamide)-LH-RH analogue, somatostatin, somatotropin, interferon, calcitonin, encephalin, endorphin, angiotensin, heparin and derivatives, synthetic analogues and/or muteins or active fragments thereof. The solvents employed for preparing the compositions in the form of particles according to the invention are those classical for pharmaceutical use such as water, aqueous solutions with different pH-values, methanol, ethanol, methylene chloride, chloroform, acetonitrile, isopropyl alcohol, acetone, methylethylketone, etc.

Agents able to modify the interface properties of the particles comprise: surface-active agents and mixtures thereof, for instance sorbitan esters, polysorbates, lecithins and other phospholipides, stearic acid, stearates and derivatives, etc. The percentage of the amphiphilic polymer relative to the biodegradable polymer may range from 30 to 50% by weight. The percentage of the agents modifying the interface properties of the particles is comprised between 0.1% and 99.9% with regard to the polymers and preferably between 0.1% and 50% by weight. The percentage of the active substance in the compositions is comprised between 1% and 50% by weight. The features of the compositions of the invention may be evaluated according to different methods, such as:

- determination of the permeability;
- determination of the surface properties by estimating the contact angle solid/liquid;
- scanning differential calorimetry to determine the thermic properties (glass transition temperature) and fusion temperature and enthalpy;
- mercury porosimetry for determining the particle dimensional distribution. The compositions in the form of particles according to the invention show, when compared to those obtained according to known techniques, important advantages present either alone or simultaneously:
- no hydrolysing agent is added, thus the polymer keeps its molecular weight;
- no chemical agent is introduced, which may exert an influence on the stability of the active agent;
- the chemical nature of the components is not modified;
- the amphiphilic polymer may be used as solubilizer of the biodegradable polymer and/or polysaccharide polymer;
- the amphiphilic polymer and the agent modifying the interface properties may be used as modulators of the solubility of the active agent.

Furthermore the obtained product exhibits the following desirable features:

- the glass transition temperature of the biodegradable or polysaccharide polymer is decreased and therefore the permeability of the same polymer is modified (either decreased or increased) depending on the percentages and molecular weights of the amphiphilic polymers employed;
- the modification of the permeability modulates both the release rate of the active substance and the degradation rate of the polymer;
- at appropriate percentage of amphiphilic polymer there are two simultaneous phases with different thermic features;
- the surface energy of the particles is decreased with resulting improved biocompatibility;
- by using suitable ratios among biodegradable or polysaccharide polymers, amphiphilic polymer and agent modifying the interface properties, the best composition may be obtained with regard to the chemical-physical features of the active substance and having the desired release rate. The compositions in the form of particles of the present invention may be employed in manufacturing different pharmaceutical formulations among which the following are cited: injectable suspensions, inhalant suspensions or powders, rectal formulations, subcutaneous implants and oral formulations. Said compositions may in any case be suspended or mixed with suitable excipients which are normal in the pharmaceutical field. The following examples of preparation of compositions according to the present invention (examples 1 to 9) and further examples of formulations according to different techniques (examples A-T) are hereinafter reported for illustrative purpose.

The characterisation of the obtained products is discussed at the end of the examples.

EXAMPLE 1.

1.5 gr co-poly (lactic-glycolic) acid (PLG 75:25) having i.v. (inherent viscosity) in CHCl₃ 0.74 dl/g (deciliters per gram) at 30°C are dissolved in 30 ml methylene chloride with amounts of amphiphilic polymer (PEG 400) and agent modifying the interface properties (Tween 80) corresponding to 10% and 0.5% relative to the PLG polymer. The solution is emulsified in 1200 ml distilled water comprising 0.1% Tween 80. Shaking is maintained until complete evaporation of

the solvent is achieved and the thus obtained particles are filtered, washed in distilled water and dried in vacuum. The size of the obtained product ranges from 1 and 10 μm .

EXAMPLE 2

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The example 1 is repeated with the difference that the used amount of Tween 80 is 1% relative to the PLG polymer.

EXAMPLE 3

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The example 1 is repeated with the difference that the used amount of Tween 80 is 1.5% relative to the PLG polymer.

EXAMPLE 4

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The example 1 is repeated with the difference that the used amount of PEG 400 is 2% relative to the PLG polymer.

EXAMPLE 5

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The example 1 is repeated with the difference that the used amount of PEG 400 is 5% relative to the PLG polymer.

EXAMPLE 6

The example 1 is repeated with the difference that the used amount of PEG 400 is 20% relative to the PLG polymer.

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EXAMPLE 7

The example 1 is repeated with the difference that the used amount of PEG 400 is 30% relative to the PLG polymer.

EXAMPLE 8

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The example 1 is repeated with the difference that the used amount of PEG 400 is 40% relative to the PLG polymer.

EXAMPLE 9

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The example 1 is repeated with the difference that the used amount of PEG 400 is 50% relative to the PLG polymer.

EXAMPLE A

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1.5 gr co-poly (lactic-glycolic) acid (PLG 75/25, i.v. in CHCl_3 0.74 dl/g at 30°C) are solved in 30 ml methylene chloride. The solution is emulsified in 1200 ml distilled water comprising 0.1% of agent modifying the interface properties (Tween 80). Shaking is carried on until complete evaporation of the solvent is achieved and the thus obtained particles are filtered, washed with distilled water and dried in vacuum. The size of the obtained product ranges from 2 to 20 μm .

EXAMPLE B

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1.5 gr co-poly (lactic-glycolic) acid (PLG 75/25, i.v. in CHCl_3 0.74 dl/g at 30°C) are solved in 30 ml methylene chloride with an amount of polyethyleneglycol (PEG 400) of 2% relative to the PLG. Said solution is emulsified in 1200 ml distilled water comprising 0.1% of Tween 80. Shaking is carried on until complete evaporation of the solvent is achieved and the thus obtained particles are filtered, washed with distilled water and dried in vacuum. The size of the obtained product ranges from 1 to 10 μm .

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EXAMPLE C

The example B is repeated with the difference that the employed amount PEG 400 is 5% relative to the PLG.

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EXAMPLE D

The example B is repeated with the difference that the employed amount PEG 400 is 10% relative to the PLG.

EXAMPLE E

The example B is repeated with the difference that the employed amount PEG 400 is 20% relative to the PLG.

EXAMPLE F

The example B is repeated with the difference that the employed amount PEG 400 is 30% relative to the PLG.

EXAMPLE G

The example B is repeated with the difference that the employed amount PEG 400 is 40% relative to the PLG.

EXAMPLE H

The example B is repeated with the difference that the employed amount PEG 400 is 50% relative to the PLG.

EXAMPLE I

1.5 gr co-poly (lactic-glycolic) acid (PLG 75/25, i.v. in CHCl_3 0.74 dl/g at 30°C) are solved in 30 ml methylene chloride with an amount of Tween 80 corresponding to the 0.5% relative to the polymer. Said solution is emulsified in 1200 ml distilled water comprising 0.1% of Tween 80. Shaking is carried on until complete evaporation of the solvent is achieved and the thus obtained particles are filtered, washed with distilled water and dried in vacuum. The size of the obtained product ranges from 1 to 10 μm .

EXAMPLE L

The example I is repeated with the difference that the employed amount Tween 80 is 1% relative to the polymer.

EXAMPLE M

The example I is repeated with the difference that the employed amount Tween 80 is 1.5% relative the polymer.

EXAMPLE N

The example I is repeated with the difference that the employed amount Tween 80 is 2.0% relative to the polymer.

EXAMPLE P

10 g polyethyleneglycol 20.000 and 50 mg Tween 80 are dissolved in 10 ml water/ethanol 50/50 v/v mixture. Said solution is dried by spray-drying and the size of the obtained particles ranges from 5 to 10 μm .

EXAMPLE Q

1.5 gr co-poly (lactic-glycolic) acid (PLG 75/25) are solved in 30 ml methylene chloride with 150 mg broxaterol base. Said solution is emulsified in 1200 ml distilled water comprising 0.1% of interface-active agent (Tween 80). Shaking is carried on until complete evaporation of the solvent is achieved and the thus obtained microparticles are filtered, washed with distilled water and dried in vacuum. The size of the obtained product are comprised from 3 to 10 μm .

EXAMPLE R

600 mg co-poly (lactic-glycolic) acid (PLG 75/25) are solved in 12 ml methylene chloride/ethanol 8/2 v/v mixture with 240 mg nicergoline. Said solution is emulsified in 400 ml aqueous solution comprising 0.1% of interface-active agent (Tween 80). Shaking is carried on until complete evaporation of the solvent is achieved and the thus obtained microparticles are filtered, washed with distilled water and dried in vacuum. The size of the obtained product are comprised from 10 to 50 μm .

EXAMPLE S

1 gr co-poly (lactic-glycolic) acid (PLG 75/25) is solved in 20 ml methylene chloride/ethanol 7/3 mixture with 50 mg adriamycin. Said solution is emulsified in 600 ml in 1% Tween 80 aqueous solution. Shaking is carried on until complete evaporation of the solvent and the thus obtained microsphere suspension is centrifuged and dried in microwave oven. The size of the obtained microspheres is comprised from 10 to 40 μm .

EXAMPLE T

1 gr co-poly (lactic-glycolic) acid (PLG 75/25) is solved in 20 ml methylene chloride. Salmon calcitonin (sCT) (25 mg) solved in the lowest necessary amount of pure acetic acid is added to the solution. Thus obtained solution is emulsified in 600 ml of 2.0% Tween 80 solution in distilled water with pH adjusted to the sCT isoelectric point. Shaking is carried on until formation of the emulsion is achieved, which is then brought in vacuum, keeping the shaking till complete evaporation of the solvent. Thus obtained microsphere suspension is centrifuged and dried in vacuum. The microspheres have size ranging from 30 to 50 μm .

CHARACTERISATION TESTS

Hereinafter there are reported the description and results of the characterisation tests of the compositions prepared according to the invention. Comparison tests with analogous compositions prepared according to known techniques are also reported.

SURFACE ENERGY FEATURES

A feature of the compositions prepared according to the present invention is the modification of the surface energy, which allows an improved biocompatibility to be obtained. The modification of the surface energy is correlated to the wettability by the following equation :

$$\gamma_{sv} = \gamma_{sl} + \gamma_{lv} \cos(\theta)$$

where:

γ_{sv} = surface energy solid/vapour
 γ_{sl} = surface energy solid/liquid
 γ_{lv} = surface energy liquid/vapour
 θ = contact angle liquid/solid.

For any material, γ_{sv} may be split into a polar component and a dispersing component according to the equation:

$$\gamma_s(\text{tot}) = \gamma_s(p) + \gamma_s(d)$$

Said components may be calculated from experimental determinations of the contact angle and thereafter they may be included into the equation for the determination of the biocompatibility associated surface energy:

$$\gamma_{sl} = \gamma_s(\text{tot}) + \gamma_l(\text{tot}) - 4 \frac{\gamma_l(p) \gamma_s(p)}{\gamma_l(p) + \gamma_s(p)} - 4 \frac{\gamma_l(d) \gamma_s(d)}{\gamma_l(d) + \gamma_s(d)}$$

where: s = solid; l = liquid.

In the present case the values considered for the liquid are those relating to water, which is comparable to the physiological fluids which are in contact with the material in vivo. The modification of the surface energy, thus of the biodegradability, is correlated to the polarity of the material, which may be expressed in percents according to the equation:

$$\% P_l = \frac{\gamma_p \times 100}{\gamma_p + \gamma_d}$$

The method involves the determination of the contact angle (teta) between the surface of the material and a polar and/or non-polar liquid; said determination is carried out with a Lorentzen & Wetter apparatus equipped with a compartment for the evaporation of the same liquid. The data relating to some compositions comprising a biodegradable polymer and different percentages of amphiphilic polymer are reported by way of example in Table 1. In Table 2 and 3 there

are reported data relating to the same biodegradable polymer in presence of an agent modifying the interface properties and the data relating to compositions comprising such a polymer, different percentages of amphiphilic polymer and the agent modifying the interface. As it can be appreciated, upon increase of the percent of the amphiphilic polymer, the surface energy of the interaction between solid and physiological liquid decreases (Tab. 1 col. 5) with consequent improved biocompatibility of the materials. Moreover the increase of the polarity (Tab. 1 col. 6) is a further indicator of the improved biocompatibility. From Table 2, column 5 and 6, the same trend as observed in the previous Table can be noted, though obtained with different percentages of the agent modifying the interface properties. From Table 3 it is evident the extent to which the association amphiphilic polymer/ agent modifying the interface properties of the particle material object of the present invention brings about a synergism, which is derivable specifically from the data of surface energy and polarity (col. 5 and 6).

THERMIC PROPERTIES

In Table 4 there are reported the thermoanalytical data relative to the compositions in the form of particles prepared according to the invention as determined using a scanning differential calorimeter Perkin-Elmer Mod. TAS 7. One of the features of the products of the invention, is that either a composite homogeneous material or a material having phases with different features may be obtained upon modification of the percentage of the amphiphilic polymer. In the first case the decrease of the glass transition (T_g) temperature and accompanying variation in the permeability of the material, which increases or decreases depending on the percentages and molecular weights of the employed amphiphilic polymer, can be evidenced by thermic analysis (col. 3, percents from 2 to 20%). In the second case two clearly distinct transition events can be observed, one relative to the T_g of the polymeric component and one relative to the fusion temperature (F_t) of the amphiphilic polymer (col. 3 and 4, percents from 30% onwards). This is particularly useful in the case where the active substance is more compatible as regard to one of the polymeric materials. In column 5 there is reported the value of the melting enthalpy of the amphiphilic polymer. The increase in value of the delta H upon increase of the PEG percentage is an indicator of the amount of PEG responsible for the phenomenon of the phase separation. The adjustment of the permeability of the particles allows the controlled release of the active substance and thus the control of its activity to be attained.

TABLE 1

Data relative to some compositions comprising a biodegradable polymer and different percents of amphiphilic polymer.						
	Col.1 % PEG	Col.2 γ_s	Col.3 γ_s	Col.4 γ_{tot}	Col.5 γ_{sl}	Col.6 % P
ES.A	0.0	12.39	30.57	42.96	24.62	28.84
ES.B	2.0	14.23	30.22	44.45	21.73	32.02
ES.C	5.0	15.27	29.08	44.35	19.98	34.44
ES.D	10.0	16.67	30.21	46.88	18.44	35.58
ES.E	20.0	20.03	30.94	50.97	14.78	39.38
ES.F	30.0	23.01	31.66	54.67	12.14	42.09
ES.G	40.0	25.35	31.57	56.91	10.12	44.53
ES.H	50.0	28.21	31.23	59.45	7.97	47.46
ES.P	100.0	39.48	32.27	71.76	3.30	55.01
% PEG = percent amphiphilic polymer relative to the biodegradable polymer. The " γ " are expressed in dyne/cm.						

TABLE 2

Data relative to some compositions comprising a biodegradable polymer and an agent modifying the interface properties.

	Col.1 % T-80	Col.2 γ_s	Col.3 γ_s	Col.4 γ_{tot}	Col.5 γ_{sl}	Col.6 % P
ES.A	0.0	12.39	30.57	42.96	24.62	28.84
ES.I	0.5	14.33	33.09	47.42	22.52	30.23
ES.L	5.0	15.27	29.08	44.35	19.98	34.44
ES.M	10.0	16.67	30.21	46.88	18.44	35.58
ES.N	20.0	20.03	30.94	50.97	14.78	39.38

The " γ " are expressed in dyne/cm.

% T-80 = percent of the agent modifying the interface properties relative to the polymer.

TABLE 3

Data relative to compositions comprising a biodegradable polymer and different percentages of amphiphilic polymer and agent modifying the interface properties.

	Col.1 % PEG % T-80	Col.2 γ_s	Col.3 γ_s	Col.4 γ_{tot}	Col.5 γ_{sl}	Col.6 % P
ES.A	0.0	12.39	30.57	42.96	24.62	28.84
ES.D	0.0	16.67	30.21	46.88	18.44	35.58
	10.0					
ES.I	0.0	14.33	33.09	47.42	22.52	30.23
	0.5					
ES.1	10.0	16.98	31.69	48.15	19.16	34.19
	0.5					
ES.2	10.0	27.74	31.53	59.27	8.38	46.80
	1.0					
ES.3	10.0	28.66	39.54	68.20	2.22	57.96
	1.5					

The % of PEG and T-80 are relative to the biodegradable polymer.

TABLE 4

Thermic properties of some products prepared according to the invention					
Col.1	Col.2 % PEG	Col.3 Tg(°C)	Col.4 Ft(°C)	Col.5 ΔH(J/g)	Notes
ES.I	0.0	25.24			
ES.4	2.0	13.47			
ES.5	5.0	10.06			
ES.1	10.0	7.87			
ES.6	20.0	6.03			
ES.7	30.0	12.80	22.10	33.74	separ. phase
ES.8	40.0	14.26	21.11	39.83	separ. phase
ES.9	50.0	25.09	4.89	51.64	separ. phase
ES.P	100.0		0.84	98.03	
% PEG relative to the PLG. Ft is the fusion temperature of PEG Each sample also comprises 0.5% T-80.					

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Pharmaceutical compositions, in the form of particles having a diameter from 0.1 and 150 μm, suitable for the controlled release of the active substance, comprising a biodegradable polymer consisting of co-poly(lactic-glycolic) acid, an amphiphilic polymer consisting of polyethyleneglycol (PEG 400), an agent modifying the interface properties and an active substance, characterized in that said particles have separate phases with different thermal characteristics when the content of said amphiphilic polymer is from 30 to 50% by weight relative to said biodegradable polymer.
2. Compositions according to claim 1, characterized in that said agent modifying the interface properties is selected from the group consisting of sorbitan esters, polysorbates, lecithins, stearic acid and stearates.
3. Compositions according to claim 1, characterized in that said active substance is selected from the group consisting of central nervous system active medicaments, cardiovasculars, hypotensives, diuretics, antiphlogistics, analgesics, antipyretics, antiasthma, bronchodilators, antitussives, mucolytics, antibiotics, chemotherapeutics, antiviral, hormones, antineoplastics, immunosuppressors, immunostimulants, proteins, polypeptides, vaccines.
4. Compositions according to claim 1, characterized in that said active substance is calcitonine.
5. Compositions according to claim 1, characterized in that said active substance is selected from the group of LH-RH analogues.
6. Compositions according to claim 1, characterized in that said active substance is (Des-Gly, D-Trp⁶, Pro⁹-ethylamide) LH-RH analogue.
7. Compositions according to claim 1, characterized in that said active substance is somatostatin.
8. Compositions according to claim 1, characterized in that said active substance is somatotropin.
9. Compositions according to claim 1, characterized in that said active substances are broxaterol and hydrochloride thereof.

10. Compositions according to claim 1, characterized in that said active substance is nicergoline.
11. Compositions according to claim 1, characterized in that said active substance is megestrol acetate.
- 5 12. Compositions according to claim 1, characterized in that said active substance is adriamycin.
13. Compositions according to claim 1, characterized in that said active substance is levonorgestrel.
14. Compositions according to claim 1, characterized in that the percentage of the agent modifying the interface prop-
10 erties is comprised between 0.1% and 50% by weight relative to the polymers.
15. Compositions according to claim 1, characterized in that the percentage of the active substance in the composition is comprised between 1% and 50% by weight.
- 15 16. Process for the preparation of pharmaceutical compositions as claimed in claim 1 characterized in that:
 - a) the polymeric compounds and the agent modifying the interface properties are co-solubilized in presence or absence of solvents;
 - b) the active substance is dissolved or dispersed in the mixture of the polymeric compounds;
 - 20 c) the obtained mixture is brought in the form of particles having diameter comprised between 0.1 and 150 μm by means of emulsifying or extruding or spray-drying or spray-congealing techniques;
 - d) said particles are optionally washed and dried according to classical methods.
17. Process according to claim 16, characterized in that in the technique of emulsifying, the outer phase of the emul-
25 sion comprises such an amount of amphiphilic polymer and/or active agent to minimize the partition.
18. Process according to claim 16, characterized in that in the technique of extruding, the mixture consisting of the poly-
meric compounds, the agent modifying the interface properties and the active substance is extruded by means of
a heat-extruder and the extruded material is granulated or micronized.
- 30 19. Process according to claim 16, characterized in that in the technique of spray-drying, the mixture consisting of the polymeric compounds, agent modifying the interface properties, active substance and solvent or solvent mixture is sprayed at temperature higher than the solvent evaporation point thus obtaining the composition in the form of par-
ticles.
- 35 20. Process according to claim 16, characterized in that in the technique of spray-congealing, the mixture consisting of the polymeric compounds, agent modifying the interface properties, active substance and solvent is sprayed in a cold air flow at temperature lower than the congealing temperature of the employed solvent and the resulting powder is lyophilized.
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Claims for the following Contracting States : ES, GR

1. Process for the preparation of pharmaceutical compositions, in the form of particles having a diameter from 0.1 and 150 μm , suitable for the controlled release of the active substance, comprising a biodegradable polymer consisting
45 of co-poly(lactic-glycolic) acid, an amphiphilic polymer consisting of polyethyleneglycol (PEG 400), an agent modifying the interface properties and an active substance, said particles having separate phases with different thermal characteristics when the content of said amphiphilic polymer is from 30 to 50% by weight relative to said biodegradable polymer, characterized in that:
 - 50 a) the polymeric compounds and the agent modifying the interface properties are co-solubilized in presence or absence of solvents;
 - b) the active substance is dissolved or dispersed in the mixture of the polymeric compounds;
 - c) the obtained mixture is brought in the form of particles having diameter comprised between 0.1 and 150 μm by means of emulsifying or extruding or spray-drying or spray-congealing techniques;
 - 55 d) said particles are optionally washed and dried according to classical methods.
2. Process according to claim 1, characterized in that in the technique of emulsifying, the outer phase of the emulsion comprises such an amount of amphiphilic polymer and/or active agent to minimize the partition.

3. Process according to claim 1, characterized in that in the technique of extruding, the mixture consisting of the polymeric compounds, the agent modifying the interface properties and the active substance is extruded by means of a heat-extruder and the extruded material is granulated or micronized.

5 4. Process according to claim 1, characterized in that in the technique of spray-drying, the mixture consisting of the polymeric compounds, agent modifying the interface properties, active substance and solvent or solvent mixture is sprayed at temperature higher than the solvent evaporation point thus obtaining the composition in the form of particles.

10 5. Process according to claim 1, characterized in that in the technique of spray-congealing, the mixture consisting of the polymeric compounds, agent modifying the interface properties, active substance and solvent is sprayed in a cold air flow at temperature lower than the congealing temperature of the employed solvent and the resulting powder is lyophilized.

15 Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

20 1. Pharmazeutische Zusammensetzungen in Form von Partikeln, welche einen Durchmesser von 0,1 bis 150 µm haben und welche für die kontrollierte Freigabe des Wirkstoffs geeignet sind, die ein biologisch abbaubares Polymer, das aus Co-Poly(milch-glykol)säure besteht, ein amphiphiles Polymer, das aus Polyethylenglykol (PEG 400) besteht, ein die Grenzflächeneigenschaften modifizierendes Agens und einen Wirkstoff enthalten, dadurch gekennzeichnet, daß die Partikel getrennte Phasen mit unterschiedlichen thermischen Charakteristika haben, wenn der Gehalt an amphiphilem Polymer 30 bis 50 Gew.%, bezogen auf das biologisch abbaubare Polymer, ist.

25 2. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß das die Grenzflächeneigenschaften modifizierende Agens aus der aus Sorbitanestern, Polysorbaten, Licitinen, Stearinsäure und Stearaten bestehenden Gruppe ausgewählt ist.

30 3. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff aus der aus wirksamen Medikamenten für das zentrale Nervensystem, kardiovaskulären Arzneimitteln, hypotonen Arzneimitteln, Diuretika, Antiphlogistika, Analgetika, Antipyretika, Arzneimitteln gegen Asthma, Bronchodilatoren, Antitussiva, Mukolytika, Antibiotika, Chemotherapeutika, antiviralen Arzneimitteln, Hormonen, Antineoplastika, Immunosuppressoren, Immunostimulantien, Proteinen, Polypeptiden, Impfstoffen bestehenden Gruppe ausgewählt ist.

35 4. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Calcitonin ist.

5. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff aus der Gruppe der LH-RH-Analoga ausgewählt ist.

40 6. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff ein (Des-Gly, D-Trp⁶, Pro⁹-Ethylenamid)-LH-RH-Analogon ist.

7. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Somatostatin ist.

45 8. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Somatotropin ist.

9. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß die Wirkstoffe Proxaterol und Hydrochlorid desselben sind.

50 10. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Nicergolin ist.

11. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Megesterolacetat ist.

55 12. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Adriamycin ist.

13. Zusammensetzungen nach Anspruch 1, dadurch gekennzeichnet, daß der Wirkstoff Levonorgestrel ist.

14. Zusammensetzungen nach Anspruch 1, dadurch **gekennzeichnet**, daß der Prozentgehalt des die Grenzflächeneigenschaften modifizierenden Agens, bezogen auf die Polymeren, zwischen 0,1 und 50 Gew.% ist.
- 5 15. Zusammensetzungen nach Anspruch 1, dadurch **gekennzeichnet**, daß der Prozentgehalt des Wirkstoffs in der Zusammensetzung zwischen 1 und 50 Gew.% beträgt.
16. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen, wie sie in Anspruch 1 beansprucht sind, dadurch **gekennzeichnet**, daß
 - 10 a) die polymeren Verbindungen und das die Grenzflächen-modifizierende Agens in Gegenwart oder Abwesenheit von Lösungsmitteln co-solubilisiert werden;
 - b) der Wirkstoff in dem Gemisch der polymeren Verbindungen aufgelöst oder dispergiert wird;
 - 15 c) das erhaltene Gemisch durch Techniken wie Emulgieren oder Extrudieren oder Sprühtrocknen oder Festwerdenlassen unter Sprühen in die Form von Partikeln, die einen Durchmesser von zwischen 0,1 und 150 µm haben, gebracht wird;
 - d) diese Partikel wahlweise mit klassischen Verfahren gewaschen und getrocknet werden.
- 20 17. Verfahren nach Anspruch 16, dadurch **gekennzeichnet**, daß bei der Technik des Emulgierens die äußere Phase der Emulsion eine solche Menge an amphiphilem Polymer und/oder Wirkstoff enthält, daß die Verteilung minimiert wird.
- 25 18. Verfahren nach Anspruch 16, dadurch **gekennzeichnet**, daß in der Technik des Extrudierens das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens und dem Wirkstoff besteht, mittels Wärmeextruder extrudiert wird, und das extrudierte Material granuliert oder mikronisiert wird.
- 30 19. Verfahren nach Anspruch 16, dadurch **gekennzeichnet**, daß in der Technik der Sprühtrocknung das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens, dem Wirkstoff und Lösungsmittel oder Lösungsmittelgemisch besteht, bei einer Temperatur, die über dem Lösungsmittelverdampfungspunkt liegt, versprüht wird, wobei die Zusammensetzung in Form von Partikeln erhalten wird.
- 35 20. Verfahren nach Anspruch 16, dadurch **gekennzeichnet**, daß in der Technik des Festwerdenlassens unter Sprühen das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens, dem Wirkstoff und dem Lösungsmittel besteht, in einen kalten Luftstrom bei einer Temperatur, die unter der Erstarrungstemperatur des verwendeten Lösungsmittels liegt, gesprüht wird, und das resultierende Pulver lyophilisiert wird.
- 40 **Patentansprüche für folgende Vertragsstaaten : ES, GR**
1. Verfahren zur Herstellung von pharmazeutischen Zusammensetzungen in Form von Partikeln, welche einen Durchmesser von 0,1 bis 150 µm haben und welche für die kontrollierte Freigabe des Wirkstoffs geeignet sind, die
 - 45 ein biologisch abbaubares Polymer, das aus Co-Poly(milch-glykol)säure besteht, ein amphiphiles Polymer, das aus Polyethylenglykol (PEG 400) besteht, ein die Grenzflächeneigenschaften modifizierendes Agens und einen Wirkstoff enthalten, wobei die Partikel getrennte Phasen mit unterschiedlichen thermischen Charakteristika haben, wenn der Gehalt an amphiphilem Polymer 30 bis 50 Gew.-%, bezogen auf das biologisch abbaubare Polymer, ist, dadurch **gekennzeichnet**, daß
 - 50 a) die polymeren Verbindungen und das die Grenzflächen-modifizierende Agens in Gegenwart oder Abwesenheit von Lösungsmitteln co-solubilisiert werden;
 - b) der Wirkstoff in dem Gemisch der polymeren Verbindungen aufgelöst oder dispergiert wird;
 - 55 c) das erhaltene Gemisch durch Techniken wie Emulgieren oder Extrudieren oder Sprühtrocknen oder Festwerdenlassen unter Sprühen in die Form von Partikeln, die einen Durchmesser von zwischen 0,1 und 150 µm haben, gebracht wird;
 - d) diese Partikel wahlweise mit klassischen Verfahren gewaschen und getrocknet werden.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß in der Technik des Emulgierens die äußere Phase der Emulsion eine solche Menge an amphiphilem Polymer und/oder Wirkstoff enthält, daß die Verteilung minimalisiert wird.
- 5 3. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß in der Technik des Extrudierens das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens und dem Wirkstoff besteht, mit einem Wärmeextruder extrudiert wird, und das extrudierte Material granuliert oder mikronisiert wird.
- 10 4. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß in der Technik der Sprühtrocknung das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens, Wirkstoff und Lösungsmittel oder Lösungsmittelgemisch besteht, bei einer Temperatur, die über dem Lösungsmittelverdampfungspunkt liegt, versprüht wird, wobei die Zusammensetzung in Form von Partikeln erhalten wird.
- 15 5. Verfahren nach Anspruch 1, dadurch **gekennzeichnet**, daß in der Technik des Festwerdenlassens unter Sprühen das Gemisch, das aus den polymeren Verbindungen, dem die Grenzflächeneigenschaften modifizierenden Agens, dem Wirkstoff und Lösungsmittel besteht, in einen kalten Luftstrom bei einer Temperatur, die unter der Temperatur des Festwerdens des verwendeten Lösungsmittels liegt, gesprüht wird, und das resultierende Pulver lyophilisiert wird.

20 Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

- 25 1. Compositions pharmaceutiques sous la forme de particules ayant un diamètre compris entre 0.1 et 150 µm, appropriées à la libération contrôlée de la substance active, comprenant un polymère biodégradable consistant en acide co-poly(lactique/glycolique), un polymère amphiphile consistant en polyéthylèneglycol (PEG 400), un agent modificateur des propriétés d'interface, et une substance active, caractérisées en ce que lesdites particules comportent des phases séparées à caractéristiques thermiques différentes lorsque la teneur en polymère amphiphile est comprise entre 30 et 50 % en poids, par rapport audit polymère biodégradable.
- 30 2. Compositions selon la revendication 1, caractérisées en ce que ledit agent modificateur de propriétés d'interface est choisi au sein du groupe comprenant les esters de sorbitane, les polysorbates, les lécithines, l'acide stéarique, et les stéarates.
- 35 3. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est choisie au sein du groupe comprenant les médicaments agissant sur le système nerveux central, les cardiovasculaires, les hypotenseurs, les diurétiques, les antiphlogistiques, les analgésiques, les antipyrétiques, les anti-asthmatiques, les bronchodilatateurs, les antitussifs, les mucolytiques, les antibiotiques, les médicaments de chimiothérapie, les antiviraux, les hormones, les antinéoplastiques, les immunosuppresseurs, les immunostimulants, les protéines, les polypeptides, les vaccins.
- 40 4. Compositions selon la revendication 1, caractérisées en ce que la substance active est la calcitonine.
- 45 5. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est choisie au sein du groupe des analogues de la LH-RH.
6. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est l'analogue (Des-Gly, D-Trp⁶, Pro⁹-éthylamide) LH-RH.
- 50 7. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est la somatostatine.
8. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est la somatotropine.
- 55 9. Compositions selon la revendication 1, caractérisées en ce que lesdites substances actives sont le broxatérol, et le chlorhydrate de celui-ci.
10. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est la nicergoline.
11. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est l'acétate de mégéstérol.

12. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est l'adriamycine.
13. Compositions selon la revendication 1, caractérisées en ce que ladite substance active est le lévonorgestrel.
- 5 14. Compositions selon la revendication 1, caractérisées en ce que le pourcentage de l'agent modificateur de propriétés d'interface est compris entre 0.1 % et 50 % en poids, par rapport aux polymères.
15. Compositions selon la revendication 1, caractérisées en ce que le pourcentage de la substance active dans la composition est compris entre 1 % et 50 % en poids.
- 10 16. Procédé de préparation de compositions pharmaceutiques selon la revendication 1, caractérisé en ce que;
 - (a) les composés polymères et l'agent modificateur de propriétés d'interface sont co-solubilisés en la présence ou en l'absence de solvants ;
 - 15 (b) la substance active est dissoute, ou dispersée dans le mélange de composés polymères ;
 - (c) le mélange obtenu est mis sous forme de particules ayant un diamètre compris entre 0.1 et 150 µm par des techniques de mise en émulsion, ou d'extrusion, ou d'atomisation, ou de spray-congélation ;
 - (d) lesdites particules sont éventuellement lavées, et séchées, selon des méthodes classiques.
- 20 17. Procédé selon la revendication 16, caractérisé en ce que dans la technique de mise en émulsion, la phase extérieure de l'émulsion contient une quantité de polymère amphiphile et/ou d'agent actif telle que le partage soit réduit au minimum.
- 25 18. Procédé selon la revendication 16, caractérisé en ce que dans la technique d'extrusion, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, et la substance active, est extrudé au moyen d'un extrudeur à chaud, et que le matériau extrudé est granulé ou micronisé.
- 30 19. Procédé selon la revendication 16, caractérisé en ce que dans la technique d'atomisation, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, la substance active, et le solvant ou la mixture de solvants, est atomisé à une température supérieure au point d'ébullition du solvant, pour donner ainsi la composition sous la forme de particules.
- 35 20. Procédé selon la revendication 16, caractérisée en ce que dans la technique de spray-congélation, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, la substance active, et le solvant, est vaporisé dans un flux d'air froid à une température plus basse que la température de solidification du solvant employé, et la poudre obtenue est lyophilisée.

Revendications pour les Etats contractants suivants : ES, GR

- 40 1. Procédé de préparation de compositions pharmaceutiques sous la forme de particules ayant un diamètre compris entre 0,1 et 150 µm, appropriées à la libération contrôlée de la substance active, comprenant un polymère biodégradable consistant en acide co-poly(lactique/glycolique), un polymère amphiphile consistant en polyéthylèneglycol (PEG 400), un agent modificateur des propriétés d'interface, et une substance active, lesdites particules comportant des phases séparées à caractéristiques thermiques différentes lorsque la teneur en polymère amphiphile est comprise entre 30 et 50 % en poids, par rapport audit polymère biodégradable, procédé caractérisé en ce que :
 - (a) les composés polymères et l'agent modificateur de propriétés d'interface sont co-solubilisés en la présence ou en l'absence de solvants ;
 - 50 (b) la substance active est dissoute, ou dispersée dans le mélange de composés polymères ;
 - (c) le mélange obtenu est mis sous forme de particules ayant un diamètre compris entre 0.1 et 150 µm par des techniques de mise en émulsion, ou d'extrusion, ou d'atomisation, ou de spray-congélation ;
 - (d) lesdites particules sont éventuellement lavées, et séchées, selon des méthodes classiques.
- 55 2. Procédé selon la revendication 1, caractérisé en ce que dans la technique de mise en émulsion, la phase extérieure de l'émulsion contient une quantité de polymère amphiphile et/ou d'agent actif telle que le partage soit réduit au minimum.

3. Procédé selon la revendication 1, caractérisé en ce que dans la technique d'extrusion, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, et la substance active, est extrudé au moyen d'un extrudeur à chaud, et que le matériau extrudé est granulé ou micronisé.

5 4. Procédé selon la revendication 1, caractérisé en ce que dans la technique d'atomisation, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, la substance active, et le solvant ou la mixture de solvants, est atomisé à une température supérieure au point d'ébullition du solvant, pour donner ainsi la composition sous la forme de particules.

10 5. Procédé selon la revendication 1, caractérisé en ce que dans la technique de spray-congélation, le mélange comprenant les composés polymères, l'agent modificateur des propriétés d'interface, la substance active, et le solvant, est vaporisé dans un flux d'air froid à une température plus basse que la température de solidification du solvant employé, et la poudre obtenue est lyophilisée.

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